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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,874	12/13/2004	Guang-Pei Chen	PC/4-32528A	1341

1095 7590 11/18/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
QAZI, SABIHA NAIM	
ART UNIT	**PAPER NUMBER**
1612	

MAIL DATE	DELIVERY MODE
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,874	CHEN ET AL.	
	Examiner	Art Unit	
	Sabiha Qazi	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Non-Final Office Action

Claims 1-14 are pending. **No** claim is allowed at this time. Amendments are entered. Finality of the action is withdrawn.

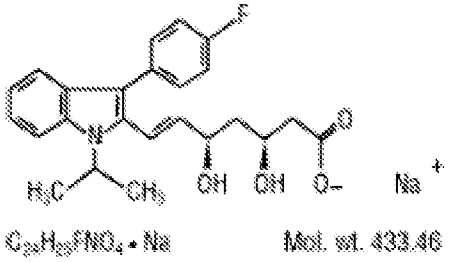
Summary of this Office Action dated Thursday, November 6, 2008

1. 35 USC § 112 (1) Written Description Rejection
2. 35 USC § 103(a) Rejections
3. Declaration and Response to Remarks
4. Communication

FLUVASTATIN Sodium (Lescol®)

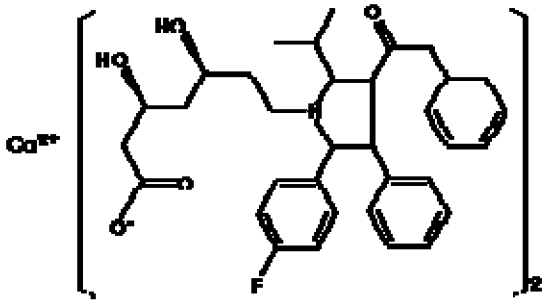
(fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4$•Na, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4$ • Na Mol. wt. 433.46

Atorvastatin, Calcium Salt (Lipitor)



Claim Rejections - 35 USC § 112 (1) Written Description Rejection

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Following reasons apply:

. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "hydrates" used herein), however, may

not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice…. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

VIPPAGUNTA (S.R. Vippagunta, et al. Adv. Drug Delivery Rev. (2001) 48, pages 3-26) teaches that, “The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition, but different internal crystal structures, and therefore, possess different physico-chemical properties.” (page 4).

"Solvates, also known as pseudo polymorphs, are crystalline solid adducts containing solvent molecules within the crystal structure, … giving rise to unique differences in the physical and pharmaceutical properties of the drug. **If the incorporated solvate is water, a solvate is termed a hydrate." (page 4).**

Vippagunta teaches that, "Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules." (page 4).

Vippagunta teaches that, "It is very important to control the crystal form of the drug during the various drug developments, because any phase

change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics." (page 5).

Vippagunta teaches that there are reversible and irreversible polymorphs (page 6), and polymorphs which are structural or conformational polymorphs (pages 7-11). Vippagunta further teaches that, "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case." (page 11).

Vippagunta teaches that "Phase changes due to hydration/dehydration and solvation/desolvation of pharmaceutical compounds during processing or in the final product may result in an unstable system that would effect the bioavailability of drug from solid dosage forms. Various types of phase changes are possible in solid-state hydrated or solvated systems in response to changes in environmental conditions… For example, some hydrated compounds may convert to an

amorphous phase upon dehydration and some may convert from a lower to a higher state of hydration yielding forms with lower solubility. Alternatively, a kinetically favored but thermodynamically unstable form may be converted during pharmaceutical processing to a more stable and less soluble form." (See page 17).

Vippagunta teaches that, "Predicting the formation of solvates or **hydrates** of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds… There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures **of hydrates** and solvates." (See page 18).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

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Claim Rejections - 35 USC § 103—1st Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over EKWURIBE et al (US Patent 6,479,692), KATHAWALA et al. (US Patent 5,354,772), and BASTIN et al. The references cited teach fluvastatin salts, and salt selection and optimization procedures for pharmaceutical new chemicals entities which embrace Applicant's claimed invention. See the entire documents.

EKWURIBE et al teaches that pharmaceutical acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples include **calcium salts.** Pharmaceutically acceptable salts defined as salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts derived from, **alkaline earth metal salts such as those of calcium and magnesium.** See lines 15-30 in col. 11.

Instant claims differ from the reference in claiming calcium salt wherein prior art specifically teaches sodium salt and alkaline earth metal salts as those of calcium and magnesium.

BASTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability, manufacturability. See the entire document especially abstract, table 1 on page 428, column 2 on page 428, Table 2 on page 429, table 4 on page 430.

KATHAWALA et al teaches indole derivatives such as fluvastatin and its salts as inhibitors of HMG-CoA reductase and method of inhibiting cholesterol biosynthesis. See claims especially claim 19-30. See example 14 which is sodium salt of fluvastatin and see examples 6, 8, 9, 22 and 39. The reference teaches sodium and potassium salts of the compounds. . Sodium salt of the claimed compound is commonly known as Fluvastatin, Sodium is a known drug. Method of preparation is also taught by the prior art.

It would have been obvious to one skilled in the art at the time of invention to prepare additional beneficial calcium salts of fluvastatin which is a known active drug in the market (as fluvastatin Sodium) because EKWURIBE et al teaches the advantages of **calcium salts that retain the**

desired biological activity of the parent compound and do not impart undesired toxicological effects. Since prior art teaches such compounds are useful for the treatment of hypercholesterolemia, atherosclerosis. The steps to prepare calcium salts by hydrolyzing the compound of formula IB to IC by alkali metal salts and then treating IC with a calcium compound to form calcium salts of 1A would have been obvious to one skilled in the art at the time invention was made. In view of the teachings of BASTIN, EKWURIBE et al and KATHAWALA et al presently claimed ca salt of the known compound would have been obvious because prior does teach the advantages of calcium salts.

In KSR v. Telefex, 82 USPQ2d 1385, 1397 (U.S. 2007), the Supreme Court has held that when there is market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person has good reason to pursue known options within his or her technical grasp. Under these conditions, "obviousness to try" such options is permissible. In this instance, a market pressure exists in the medical/pharmaceutical **industries to prepare salts with better bioavailabily, stability, solubility** Accordingly, it would have been obvious to **have**

See KSR Supreme Court of United States Decision (Decided April 30, 2007, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al. No. 04-1350) where it states that "However, the issue is not whether a person skilled in the art had the motivation to combine the electronic control with an adjustable pedal assembly, but whether a person skilled in the art had the motivation to attach the electronic control to the support bracket of pedal assembly". In the present case preparation of calcium salts of known excellent drug fluvastatin Sodium available in the market would have been obvious to one skilled in the art at the time the invention was made.

Claims 13 is drawn to a pharmaceutical composition and claim 14 is drawn to a method for treating hypercholesterolemia, hyperlipoproteinemia, dyslipidemia and atherosclerosis by the compounds of claim 7. The compound fluvatatin is known for the same uses and is in market this is covered by the formula 1A and is considered obvious over the prior art of record. Further claim 6 includes hydrates and various other compounds and is rejected under written description.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103—2nd Rejection

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Der SCHAAF et al. (WO 02/36563) and EKWURIBE et al (US Patent 6,479,692) and BASTIN et al. (Drug Delivery Reviews, 892 reference).

The van Der SCHAAF et al reference teaches various crystalline forms of fluvastatin sodium, A, B1, B2, C, D and E. The advantages of these **crystalline forms** that these can be better handled and are more stable at normal environmental humidity levels. Further these crystalline forms can be obtained from aqueous media without the risk of residual organic solvents. See the entire document especially page 1, lines 1-1-22 on pagex2, lines 1-6 on page 4, examples and claims. The X-Ray powder diffraction of each crystalline form has been taught. The reference further

teaches that crystalline polymorphs of the 3R,5S-enantiomer are preferred, lines 9-10 on page 4.

EKWURIBE et al teaches that pharmaceutical acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples include calcium salts. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, lactic acid, tartaric acid, succinic acid, maelic acid, ascorbic acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, **alkaline earth metal salts such as those of calcium and magnesium.** See lines 15-30 in col. 11.

Instant claims differ from the reference in claiming a calcium salt wherein prior art teaches sodium salt.

BASTIN teaches a salt selection and optimization procedures for pharmaceutical new chemical entities. It further teaches that selection of salts is useful for development of dosage forms with good bioavailability, stability, manufacturability. See the entire document especially abstract, table 1 on page 428, column 2 on page 428, Table 2 on page 429, table 4 on page 430.

It would have been obvious to one skilled in the art to prepare ant salt of fluvastin because first, EKWURIBE teaches salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Second, since the crystalline form of fluvastatin sodium is an excellent drug taught by van Der SCHAAF et al. (WO 02/36563) for the treatment various diseases, it seems obvious to prepare any salt such as sodium because the salts are expected to retain the biological activity. Third, one would be motivated to prepare any salt of fluvastatin such as calcium salts in any crystalline forms because fourth, SCHAAF teaches the advantages of the crystalline forms that they can be better handled and are more stable at normal environmental humidity

levels. Fifth, these crystalline forms can be obtained from aqueous media without the risk of residual organic solvents.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Declaration and Response to Remarks

Finality of the action is withdrawn. The declaration filed on 3/15/08 has been considered by the Examiner. The claimed invention must compared, however, with the closest subject matter that exists in the prior art. See MPEP 712.02(e). The comparison must be made under identical conditions. The data is not clear and present technical problems. Further, the results are not unexpected. In the present case the comparison is not a side by side comparison. The compound exist is various crystalline polymorphic forms as has been taught by WO 02/36563. The reference teaches various crystalline forms of fluvastatin. These forms are defines by form A, form B, form C, form D and from E. Differences between the claimed invention and the prior art are expected to result in some

differences in properties. The properties does not differ to such an extent that the difference is really unexpected. The unexpected property or result must actually be unexpected and of statistical and practical significance. See MPEP 716.02(a).

Applicant argues that "calcium salt of fluvastatin is considerably less hygroscopic than sodium salt, i.e. 2.8% gain at 84% RH (relative humidity) vs. 26% gain at 84% RH respectively". It is unclear why powdered form of sodium salt was used when crystalline form has been taught by the prior art (WO 02/36563) which is more stable. The reference teaches stable monosodium salts of fluvastatin containing 60-75% RH. Further the process of making and type of crystalline form are not disclosed. There different form of crystalline forms.

The claimed invention may be compared with prior art that is closer than that applied by the examiner. In re Holladay, 584 F.2d 384 (CCPA 1978).

Even if the comparison is correct as argued the data does not commensurate with scope of the claimed subject matter which includes large number of compounds.

Claimed invention has been considered obvious for the reasons cited above. In KSR v. Telefex, 82 USPQ2d 1385, 1397 (U.S. 2007), the Supreme Court has held that when there is market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person has good reason to pursue known options within his or her technical grasp. Under these conditions, "obviousness to try" such options is permissible. In this instance, a market pressure exists in the medical/pharmaceutical **industries to find an improved form of drug.** Accordingly, it would have been obvious to prepare a calcium salt or any other salt using methods available at the time the invention was filed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/

Primary Examiner, Art Unit 1612